REMARKS

STATUS OF THE CLAIMS

Claims 49 and 75 have been amended. Following entry of the amendments claims 49 – 51, 56 – 58, 67, 69 – 72, 75, and 76 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Exemplary support for the amendments to claims 49 and 75 are found, e.g., in the following places: p. 6, lines 4-8; p. 8, lines 20-29; p. 9, lines 1-21; p. 10, lines 28-32; p. 11, lines 1-12; p. 12, lines 18-26; p. 13, line 1 through p. 14, line 24; p. 31, lines 21-31; p. 33, line 1 through p. 36, line 4; p. 56, line 31 through p.58, line 21; p. 61, line 30 through p. 63, line 14, Fig. 5, and Fig. 6.

The amendments to the claims therefore add no new matter.

APPLICANTS' SUMMARY OF TELEPHONIC INTERVIEW CONDUCTED OCTOBER 19, 2005

Applicants' representative thanks Examiner Brannock for the courtesy extended during the telephonic interview conducted October 19, 2005. During the interview, Applicants' representative advised the Examiner of the issuance of U.S. Patent No. 6,955,887 to Adler *et al.* Applicants' representative indicated that he would file a response to the September 15, 2005 Office Action to address the remaining outstanding rejections by providing evidence based on publications by Jiang *et al.* that tended to prove that it is within the level of ordinary skill to prepare artificial sequences that are within the scope of the instant claims without the exercise of undue experimentation. Examiner Brannock indicated that upon receipt of the response, the finality of the September 15, 2005 Office Action would be withdrawn and a rejection based upon the Adler *et al.* patent would be issued.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 49-51 and 56-58, 67, 69-72, 75, and 76 remain rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the phrase "determining the functional effect." The Examiner states that "although the specification recites several examples of

"functional effects" the skilled artisan could not be sure whether or not he or she was practicing the claimed invention because of the presence of such an ambiguous term." Office Action at page 2. Applicants' arguments included in the response mailed July 28, 2005 were considered by the Examiner but not deemed persuasive. *Id.* at 3. While not agreeing with the Examiner's position, and in an effort to expedite prosecution, Applicants have amended claims 49 and 75 (from which the remaining rejected claims depend) to recite that the functional effect is binding to or an effect on receptor activity. Applicants believe that ordinarily skilled artisan will readily recognize the metes and bounds of the amended claim language and respectfully request withdrawal of the rejection.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 49-51, 56-58, 67, 69-72, 75, and 76 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Office Action at page 4.

The Examiner's position is that the specification is enabling for methods of identifying activators and inhibitors of sweet taste signal transduction, comprising a taste cell receptor composed of a heterodimer of SEQ ID NO: 9 and 15, wherein the receptor is present on the surface of a cell, and wherein the receptor is coupled to a Gα15 or Gα16 protein, but does not reasonably provide enablement for methods employing artificially constructed variants of SEQ ID NO: 9 and 15. *Id.* The Examiner has further suggested that in the response mailed July 28, 2005, Applicant provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change, and the nature and extent of changes that can be made in these positions. *Id.* Applicants incorporate by reference their response to the rejections under 35 U.S.C. § 112, first paragraph filed in their July 28, 2005 response, and now provide additional evidence (*see* Appendix I) that the art is sufficiently predictable to fully enable the scope of the pending claims. That evidence is based on two publications by Jiang *et al.*,

published earlier this year[1], that support arguments included in Applicant's July 28, 2005 response.

Jiang *et al.* constructed artificial sequences that included part human and part mouse T1R3 sequence, and showed that these artificial sequences retain function when paired with human T1R2 sequences. As Table 1 in Appendix I shows, those artificial sequences ranged from a low of 72.8% to a high of 96.6% sequence identity with the human T1R3 sequence. This illustrates that the T1R3 receptor can tolerate sequence changes affecting up to about 27% of the wild-type sequence and still retain function.

Second, Applicants argued in the July 28, 2005 response that the multiple sequences disclosed in the specification could readily be aligned to lead the ordinarily skilled artisan to identify regions where substitutions could likely be tolerated, and to those that could not. Applicants provided alignments of the sequences disclosed in the specification and argued as follows:

> Based on these sequence disclosures, the suggestion to use a conservatively modified variant, and explicit disclosure of conservative amino acid substitutions, an ordinarily skilled artisan would readily be able to carry out a sequence alignment (as, *e.g.*, known to one of ordinary skill and, *e.g.*, taught by the specification at page 16, line 10-page 17, line 16) and identify residues tolerant to conservative substitution amongst the disclosed sequences, as well as residues that are absolutely invariant and so unlikely to tolerate any substitution. Such exemplary alignments have been carried out by Applicants and are included as Appendices IV (T1R2 sequences) and V (T1R3 sequences) to [the paper filed July 28, 2005].[2]

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[1] Jiang *et al.* (2005a), "Lactisole Interacts with the Transmembrane Domains of Human T1R3 to Inhibit Sweet Taste," *J. Biol. Chem.* **280(15)**:15238-15246; and Jiang *et al.* (2005b), "Identification of the Cyclamate Interaction Site within the Transmembrane Domain of the Human Sweet Taste Receptor Subunit T1R3," *J. Biol. Chem.* **280(40)**:34296-34305 (both publications are included with the instantly-filed IDS).

[2] The invariant residues and conserved substitutions are indicated with symbols below the aligned sequences found in Appendices IV and V [of the response filed July 28, 2005]. Residues that are identical in each aligned sequence are indicated with the symbol "*", residues that are conservatively substituted are indicated with the symbol ":", and residues that are semi-conservatively substituted are indicated with the symbol ".". *See* ClustalW help file (Appendix VI) at p. 4 under "Consensus Symbols" heading.

> The alignments provide additional evidence that the ordinarily skilled artisan would be able to make functional T1R2 and T1R3 polypeptides sequences that are "at least 90% identical" to the exemplified sequences in view of the exemplified sequence divergence. *See* the last column in the "Scores Table" on the first page of Appendices IV, showing identities amongst exemplified sequences ranging from 69% to 99%. Thus, by exercise of no more than ordinary skill, an artisan having the benefit of the disclosure would be able to construct additional functional sequences within the scope of the claimed invention.

July 28, 2005 Response at pp. 11-12.

In the Office Action mailed September 15, 2005, the Examiner cited again to Bowie's teaching that "functionally important residues should be conserved in sets of active sequences, but it is not possible to decide whether a side chain is functionally or structurally important just because it is invariant or conserved..." The Examiner then suggested that the sequence data in the specification leaves the Artisan with essentially random trial and error experimentation to try to find positions which are tolerant to change. Office Action at pp. 7-8.

Analysis of mutagenesis experiments reported in the enclosed Jiang *et al.* publications provides evidence that T1R3 behaves in the manner suggested by Applicants in their July 28, 2005 Response. As Table 2 in Appendix I illustrates, there is a notable correlation between loss of function following mutation of a conserved residue, and retention of function following mutation of a non-conserved residue. These results provide further evidentiary support to Applicants' argument that sequence alignments would correctly guide the skilled artisan in making functional artificial T1R sequences.

As for the Examiner's argument that the specification fails to provide sufficient enablement for claims not limited to cells expressing the Gα15 or Gα16 G proteins (both of which are taught in the specification), Applicants respectfully ask for reconsideration of their argument set forth in the July 28, 2005 response at p. 12 in view of the fact that the Jiang *et al.* publications demonstrate that functional assays can be carried out using yet another G protein (Gα16-gust44 – a chimeric G protein and subunit containing the last 44 amino acids of gustducin; *see* Jiang *et al.* 2000(a) at 15239, and 2005(b) at 34297).

In summary, Applicants respectfully submit that analysis of the Wands factors as set forth in the July 28, 2005 response, as well as the evidence now submitted based on the Jiang *et al.*

Appendix I

Analysis of Data Reported in Jiang *et al.* 2005(a) and 2005(b)

Percent identity was determined between wild type human T1R3 sequences and chimeras reported in Jiang *et al.* 2005(a) and Jiang *et al.* 2005(b)[1]. Jiang *et al.* constructed artificial (chimeric) sequences and tested them in functional assays to localize sequence regions responsible for observed differences between human and mouse T1R2 + T1R3 receptors' responses to lactisole (Jiang *et al.* 2005(a)) and to cyclamate (Jiang *et al.* 2005(b)). Applicants carried out sequence analysis to determine the percent identity of the chimeras with the parent human sequence. Those results are presented in Table 1.

Alanine scanning and other mutagenesis experiments also were reported in Jiang *et al.* 2005(a) and 2005(b). Applicants analyzed those results to determine whether the mutated residues were in conserved or non-conserved regions, and to determine whether a correlation existed as between mutation of conserved residues with loss of function. Those results are presented in Table 2. The amino acid alignments supporting Table 1 are presented at the end of this Appendix.

Table 1

Chimera	% Human Identity
mT1R3h.548-852	81.2%
mT1R3h.568-852	80.4%
h.1-812mT1R3	96.6%
mT1R3h.729-787	72.8%

[1] Jiang *et al.* (2005a), "Lactisole Interacts with the Transmembrane Domains of Human T1R3 to Inhibit Sweet Taste," *J. Biol. Chem.* 280(15):15238-15246; and Jiang *et al.* (2005b), "Identification of the Cyclamate Interaction Site within the Transmembrane Domain of the Human Sweet Taste Receptor Subunit T1R3," *J. Biol. Chem.* 280(40):34296-34305. Both references are included in the instantly-filed IDS.

Table 2

Contruct name	Reference	Conserved between Human and Mouse	Functional
V788A	Jiang *et al.* 2005(b)	N	Y
L789Y	Jiang *et al.* 2005(b)	N	Y
R790Q	Jiang *et al.* 2005(b)	N	N
L7981	Jiang *et al.* 2005(b)	N	Y
L800V	Jiang *et al.* 2005(b)	N	Y
V802A	Jiang *et al.* 2005(b)	N	Y
A807V	Jiang *et al.* 2005(b)	N	Y
A808T	Jiang *et al.* 2005(b)	N	Y
F730L	Jiang *et al.* 2005(b)	N (F in Human L in Mouse)	REDUCED
A733V	Jiang *et al.* 2005(b)	N (A in Human V in Mouse)	Y
A735I	Jiang *et al.* 2005(b)	N (A in Human I in Mouse)	Y
T739M	Jiang *et al.* 2005(b)	N (T in Human M in Mouse)	Y
Q636A	Jiang *et al.* 2005(b)	Y (Q in Human Q in Mouse)	N
S640A	Jiang *et al.* 2005(b)	N (S in Human A in Mouse)	Y
H641A	Jiang *et al.* 2005(b)	Y (H in Human H in Mouse)	REDUCED
L644A	Jiang *et al.* 2005(b)	Y (L in Human L in Mouse)	N
T645A	Jiang *et al.* 2005(b)	Y	N

Contruct name	Reference	Conserved between Human and Mouse	Functional
H721A	Jiang *et al.* 2005(b)	Y	N
R723A	Jiang *et al.* 2005(b)	N (R in Human H in Mouse)	REDUCED
S729A	Jiang *et al.* 2005(b)	Y	REDUCED
H734A	Jiang *et al.* 2005(b)	Y	N
Y771A	Jiang *et al.* 2005(b)	Y	N
W775A	Jiang *et al.* 2005(b)	Y	N
V776A	Jiang *et al.* 2005(b)	Y	REDUCED
F778A	Jiang *et al.* 2005(b)	Y	N
V779A	Jiang *et al.* 2005(b)	Y	REDUCED
L782A	Jiang *et al.* 2005(b)	Y	N
Q794A	Jiang *et al.* 2005(b)	Y	N
I805A	Jiang *et al.* 2005(b)	Y	N
V788A	Jiang *et al.* 2005(a)	N (V in Human A in Mouse)	Y
R790Q	Jiang *et al.* 2005(a)	N (R in Human Q in Mouse)	Y
L798I	Jiang *et al.* 2005(a)	N (L in Human I in Mouse)	Y
L800V	Jiang *et al.* 2005(a)	N (L in Human V in Mouse)	N
V802A	Jiang *et al.* 2005(a)	N (V in Human A in Mouse)	Y
A807V	Jiang *et al.* 2005(a)	N (A in Human V in Mouse)	Y

Contruct name	Reference	Conserved between Human and Mouse	Functional
A808T	Jiang *et al.* 2005(a)	N (A in Human T in Mouse)	Y
F730L	Jiang *et al.* 2005(a)	N (F in Human L in Mouse)	REDUCED
A733V	Jiang *et al.* 2005(a)	N (A in Human V in Mouse)	Y
A735I	Jiang *et al.* 2005(a)	N (A in Human I in Mouse)	Y
T739M	Jiang *et al.* 2005(a)	N (T in Human M in Mouse)	Y
Q636A	Jiang *et al.* 2005(a)	Y	N
S640A	Jiang *et al.* 2005(a)	N	Y
H641A	Jiang *et al.* 2005(a)	Y	REDUCED
L644A	Jiang *et al.* 2005(a)	Y	N
T645A	Jiang *et al.* 2005(a)	Y	N
H721A	Jiang *et al.* 2005(a)	Y	N
R723A	Jiang *et al.* 2005(a)	N (R in Human H in Mouse)	REDUCED
S729A	Jiang *et al.* 2005(a)	Y	REDUCED
H734A	Jiang *et al.* 2005(a)	Y	N
Y771A	Jiang *et al.* 2005(a)	Y	N
W775A	Jiang *et al.* 2005(a)	Y	N
V776A	Jiang *et al.* 2005(a)	Y	REDUCED
F778A	Jiang *et al.* 2005(a)	Y	N
V779A	Jiang *et al.* 2005(a)	Y	REDUCED

Contruct name	Reference	Conserved between Human and Mouse	Functional
L782A	Jiang *et al.* 2005(a)	Y	N
Q794A	Jiang *et al.* 2005(a)	Y	N
I805A	Jiang *et al.* 2005(a)	Y	N

mT1R3h.548-852

81.2% identity in 856 residues overlap; Score: 3565.0; Gap frequency: 1.9%

```
mT1R3h.548      5 AIMGLSLAAFLELGMGASLCLSQQFKAQGDYILGGLFPLGSTEEATLNQRTQPNSILCNR
hT1R3,          5 AVLGLSLWALLHPGTGAPLCLSQQLRMKGDYVLGGLFPLGEAEEAGLRSRTRPSSPVCTR
                  *  **** * *  * ** ******    *** ********  *** *  ** * *  * *

mT1R3h.548     65 FSPLGLFLAMAMKMAVEEINNGSALLPGLRLGYDLFDTCSEPVVTMKSSLMFLAKVGSQS
hT1R3,         65 FSSNGLLWALAMKMAVEEINNKSDLLPGLRLGYDLFDTCSEPVVAMKPSLMFLAKAGSRD
                  **  **  * ********** * ********************** ** ******* **

mT1R3h.548    125 IAAYCNYTQYQPRVLAVIGPHSSELALITGKFFSFFLMPQVSYSASMDRLSDRETFPSFF
hT1R3,        125 IAAYCNYTQYQPRVLAVIGPHSSELAMVTGKFFSFFLMPQVSYGASMELLSARETFPSFF
                  ***************************  *************** ***  ** ********

mT1R3h.548    185 RTVPSDRVQLQAVVTLLQNFSWNWVAALGSDDDYGREGLSIFSSLANARGICIAHEGLVP
hT1R3,        185 RTVPSDRVQLTAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIAHEGLVP
                  ********** *   *** * *********** *** ****** ** ************

mT1R3h.548    245 QHDTSGQQLGKVLDVLCQVNQSKVQVVVLFASARAVYSLFSYSIHHGLSPKVWVASESWL
hT1R3,        245 LPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWVASEAWL
                        **** *** ***** **** ****  *   ** ***   ********** **

mT1R3h.548    305 TSDLVMTLPNIARVGTVLGFLQRGALLPEFSHYVETHLALAADPAFCASLNA-ELDLEEH
hT1R3,        305 TSDLVMGLPGMAQMGTVLGFLQRGAQLHEFPQYVKTHLALATDPAFCSALGEREQGLEED
                  ****** **  *  *********** * **  ** ****** *****  *   *  ***

mT1R3h.548    364 VMGQRCPQCDDIMLQNLSSGLLQNLSAGQLHHQIFATYAAVYSVAQALHNTLQCNVSHCH
hT1R3,        365 VVGQRCPQCDCITLQNVSAGLN--------HHQTFSVYAAVYSVAQALHNTLQCNASGCP
                  * ******** * *** * **          *** *  ******************** * *

mT1R3h.548    424 VSEHVLPWQLLENMYNMSFHARDLTLQFDAEGNVDMEYDLKMWVWQSPTPVLHTVGTFNG
hT1R3,        417 AQDPVKPWQLLENMYNLTFHVGGLPLRFDSSGNVDMEYDLKLWVWQGSVPRLHDVGRFNG
                      * **********  **   * * **  ********** ****   * ** ** ***

mT1R3h.548    484 TLQLQQSKMYW--PGNQVPVSQCSRQCKDGQVRRVKGFHSCCYDCVDCKAGSYRKHPDDF
hT1R3,        477 SLRTERLKIRWHTSDNQKPVSRCSRQCQEGQVRRVKGFHSCCYDCVDCEAGSYRQNPDDI
                   *     *  *    ** *** *****  ******************** *****  ***

mT1R3h.548    542 TCTPC-----NPERSTRCFRRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLFVHHRDS
hT1R3,        537 ACTFCGQDEWSPERSTRCFRRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLFVHHRDS
                   ** *      ************************************************

mT1R3h.548    597 PLVQASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLSTLFLQAA
hT1R3,        597 PLVQASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLSTLFLQAA
                  ************************************************************

mT1R3h.548    657 EIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTDWHMLPT
hT1R3,        657 EIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTDWHMLPT
                  ************************************************************
```

```
mT1R3h.548    717 EALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGCYNRARGLTFAMLAYFITWV
hT1R3,        717 EALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGCYNRARGLTFAMLAYFITWV
                  ************************************************************

mT1R3h.548    777 SFVPLLANVQVVLRPAVQMGALLLCVLGILAAFHLPRCYLLMRQPGLNTPEFFLGGGPGD
hT1R3,        777 SFVPLLANVQVVLRPAVQMGALLLCVLGILAAFHLPRCYLLMRQPGLNTPEFFLGGGPGD
                  ************************************************************

mT1R3h.548    837 AQGQNDGNTGNQGKHE
hT1R3,        837 AQGQNDGNTGNQGKHE
                  ****************
```

mT1R3h.568-852

80.4% identity in 856 residues overlap; Score: 3529.0; Gap frequency: 1.9%

```
mT1R3h.568      5 AIMGLSLAAFLELGMGASLCLSQQFKAQGDYILGGLFPLGSTEEATLNQRTQPNSILCNR
hT1R3,          5 AVLGLSLWALLHPGTGAPLCLSQQLRMKGDYVLGGLFPLGEAEEAGLRSRTRPSSPVCTR
                  *  **** * *  * ** ******    *** ********  *** *  ** * *  * *

mT1R3h.568     65 FSPLGLFLAMAMKMAVEEINNGSALLPGLRLGYDLFDTCSEPVVTMKSSLMFLAKVGSQS
hT1R3,         65 FSSNGLLWALAMKMAVEEINNKSDLLPGLRLGYDLFDTCSEPVVAMKPSLMFLAKAGSRD
                  **  **  * ********** * ********************** ** ******* **

mT1R3h.568    125 IAAYCNYTQYQPRVLAVIGPHSSELALITGKFFSFFLMPQVSYSASMDRLSDRETFPSFF
hT1R3,        125 IAAYCNYTQYQPRVLAVIGPHSSELAMVTGKFFSFFLMPQVSYGASMELLSARETFPSFF
                  ************************** ************** ***  ** ********

mT1R3h.568    185 RTVPSDRVQLQAVVTLLQNFSWNWVAALGSDDDYGREGLSIFSSLANARGICIAHEGLVP
hT1R3,        185 RTVPSDRVQLTAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIAHEGLVP
                  ********** *   *** * ********** *** ****** ** **************

mT1R3h.568    245 QHDTSGQQLGKVLDVLCQVNQSKVQVVVLFASARAVYSLFSYSIHHGLSPKVWVASESWL
hT1R3,        245 LPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWVASEAWL
                        **** *** ***** **** ****  *   ** ***   ********** **

mT1R3h.568    305 TSDLVMTLPNIARVGTVLGFLQRGALLPEFSHYVETHLALAADPAFCASLNA-ELDLEEH
hT1R3,        305 TSDLVMGLPGMAQMGTVLGFLQRGAQLHEFPQYVKTHLALATDPAFCSALGEREQGLEED
                  ****** **  *  ********** * **  ** ****** *****  *   *  ***

mT1R3h.568    364 VMGQRCPQCDDIMLQNLSSGLLQNLSAGQLHHQIFATYAAVYSVAQALHNTLQCNVSHCH
hT1R3,        365 VVGQRCPQCDCITLQNVSAGLN--------HHQTFSVYAAVYSVAQALHNTLQCNASGCP
                  * ******** * *** * **          *** *  ****************** * *

mT1R3h.568    424 VSEHVLPWQLLENMYNMSFHARDLTLQFDAEGNVDMEYDLKMWVWQSPTPVLHTVGTFNG
hT1R3,        417 AQDPVKPWQLLENMYNLTFHVGGLPLRFDSSGNVDMEYDLKLWVWQGSVPRLHDVGRFNG
                      * **********  **   * * **  ********** ****   * ** ** ***

mT1R3h.568    484 TLQLQQSKMYW--PGNQVPVSQCSRQCKDGQVRRVKGFHSCCYDCVDCKAGSYRKHPDDF
hT1R3,        477 SLRTERLKIRWHTSDNQKPVSRCSRQCQEGQVRRVKGFHSCCYDCVDCEAGSYRQNPDDI
                   *     *  *    ** *** *****  ****************** *****  ***

mT1R3h.568    542 TCTPCNQDQWSPEKSTACLPRRPKFLA-----VLLLLLLLSLALGLVLAALGLFVHHRDS
hT1R3,        537 ACTFCGQDEWSPERSTRCFRRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLFVHHRDS
                   ** * ** **** ** *  **  ***      ****************************

mT1R3h.568    597 PLVQASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLSTLFLQAA
hT1R3,        597 PLVQASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLSTLFLQAA
                  ************************************************************

mT1R3h.568    657 EIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTDWHMLPT
hT1R3,        657 EIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTDWHMLPT
                  ************************************************************

mT1R3h.568    717 EALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGCYNRARGLTFAMLAYFITWV
hT1R3,        717 EALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGCYNRARGLTFAMLAYFITWV
                  ************************************************************
```

```
mT1R3h.568    777 SFVPLLANVQVVLRPAVQMGALLLCVLGILAAFHLPRCYLLMRQPGLNTPEFFLGGGPGD
hT1R3,        777 SFVPLLANVQVVLRPAVQMGALLLCVLGILAAFHLPRCYLLMRQPGLNTPEFFLGGGPGD
                  ************************************************************

mT1R3h.568    837 AQGQNDGNTGNQGKHE
hT1R3,        837 AQGQNDGNTGNQGKHE
                  ****************
```

h.1-812mT1R3

96.6% identity in 858 residues overlap; Score: 4346.0; Gap frequency: 0.6%

```
h.1-812mT1      1 MLGPAVLGLSLWALLHPGTGAPLCLSQQLRMKGDYVLGGLFPLGEAEEAGLRSRTRPSSP
hT1R3,          1 MLGPAVLGLSLWALLHPGTGAPLCLSQQLRMKGDYVLGGLFPLGEAEEAGLRSRTRPSSP
                  ************************************************************

h.1-812mT1     61 VCTRFSSNGLLWALAMKMAVEEINNKSDLLPGLRLGYDLFDTCSEPVVAMKPSLMFLAKA
hT1R3,         61 VCTRFSSNGLLWALAMKMAVEEINNKSDLLPGLRLGYDLFDTCSEPVVAMKPSLMFLAKA
                  ************************************************************

h.1-812mT1    121 GSRDIAAYCNYTQYQPRVLAVIGPHSSELAMVTGKFFSFFLMPQVSYGASMELLSARETF
hT1R3,        121 GSRDIAAYCNYTQYQPRVLAVIGPHSSELAMVTGKFFSFFLMPQVSYGASMELLSARETF
                  ************************************************************

h.1-812mT1    181 PSFFRTVPSDRVQLTAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIAHE
hT1R3,        181 PSFFRTVPSDRVQLTAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIAHE
                  ************************************************************

h.1-812mT1    241 GLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWVAS
hT1R3,        241 GLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWVAS
                  ************************************************************

h.1-812mT1    301 EAWLTSDLVMGLPGMAQMGTVLGFLQRGAQLHEFPQYVKTHLALATDPAFCSALGEREQG
hT1R3,        301 EAWLTSDLVMGLPGMAQMGTVLGFLQRGAQLHEFPQYVKTHLALATDPAFCSALGEREQG
                  ************************************************************

h.1-812mT1    361 LEEDVVGQRCPQCDCITLQNVSAGLNHHQTFSVYAAVYSVAQALHNTLQCNASGCPAQDP
hT1R3,        361 LEEDVVGQRCPQCDCITLQNVSAGLNHHQTFSVYAAVYSVAQALHNTLQCNASGCPAQDP
                  ************************************************************

h.1-812mT1    421 VKPWQLLENMYNLTFHVGGLPLRFDSSGNVDMEYDLKLWVWQGSVPRLHDVGRFNGSLRT
hT1R3,        421 VKPWQLLENMYNLTFHVGGLPLRFDSSGNVDMEYDLKLWVWQGSVPRLHDVGRFNGSLRT
                  ************************************************************

h.1-812mT1    481 ERLKIRWHTSDNQKPVSRCSRQCQEGQVRRVKGFHSCCYDCVDCEAGSYRQNPDDIACTF
hT1R3,        481 ERLKIRWHTSDNQKPVSRCSRQCQEGQVRRVKGFHSCCYDCVDCEAGSYRQNPDDIACTF
                  ************************************************************

h.1-812mT1    541 CGQDEWSPERSTRCFRRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLFVHHRDSPLVQ
hT1R3,        541 CGQDEWSPERSTRCFRRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLFVHHRDSPLVQ
                  ************************************************************

h.1-812mT1    601 ASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLSTLFLQAAEIFV
hT1R3,        601 ASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLSTLFLQAAEIFV
                  ************************************************************

h.1-812mT1    661 ESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTDWHMLPTEALV
hT1R3,        661 ESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTDWHMLPTEALV
                  ************************************************************

h.1-812mT1    721 HCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGCYNRARGLTFAMLAYFITWVSFVP
hT1R3,        721 HCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGCYNRARGLTFAMLAYFITWVSFVP
                  ************************************************************
```

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h.l-812mT1    781 LLANVQVVLRPAVQMGALLLCVLGILAAFHLPTFHLPKCYVLLWLPKLNTQEFFLGRNAK
hT1R3,        781 LLANVQVVLRPAVQMGALLLCVLGILAAFHLP-----RCYLLMRQPGLNTPEFFLGGGPG
                  ********************************      ** *   * *** *****

h.l-812mT1    841 KAADENSGGGEAAQEHNE
hT1R3,        836 DAQGQNDGNTGNQGKHEE
                    *   * *       * *
```

mT1R3h.729-787

72.8% identity in 852 residues overlap; Score: 3125.0; Gap frequency: 2.5%

```
mT1R3h.729      5 AIMGLSLAAFLELGMGASLCLSQQFKAQGDYILGGLFPLGSTEEATLNQRTQPNSILCNR
hT1R3,          5 AVLGLSLWALLHPGTGAPLCLSQQLRMKGDYVLGGLFPLGEAEEAGLRSRTRPSSPVCTR
                  *  **** * *  * ** ******    *** ********  *** *  ** * *  * *

mT1R3h.729     65 FSPLGLFLAMAMKMAVEEINNGSALLPGLRLGYDLFDTCSEPVVTMKSSLMFLAKVGSQS
hT1R3,         65 FSSNGLLWALAMKMAVEEINNKSDLLPGLRLGYDLFDTCSEPVVAMKPSLMFLAKAGSRD
                  **  **  * ********** * ********************** ** ******* **

mT1R3h.729    125 IAAYCNYTQYQPRVLAVIGPHSSELALITGKFFSFFLMPQVSYSASMDRLSDRETFPSFF
hT1R3,        125 IAAYCNYTQYQPRVLAVIGPHSSELAMVTGKFFSFFLMPQVSYGASMELLSARETFPSFF
                  ************************** ***************** ***  ** ********

mT1R3h.729    185 RTVPSDRVQLQAVVTLLQNFSWNWVAALGSDDDYGREGLSIFSSLANARGICIAHEGLVP
hT1R3,        185 RTVPSDRVQLTAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIAHEGLVP
                  ********** *   *** * *********** *** ****** ** *************

mT1R3h.729    245 QHDTSGQQLGKVLDVLCQVNQSKVQVVVLFASARAVYSLFSYSIHHGLSPKVWVASESWL
hT1R3,        245 LPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWVASEAWL
                        **** *** ***** **** ****  *   ** ***   ********** **

mT1R3h.729    305 TSDLVMTLPNIARVGTVLGFLQRGALLPEFSHYVETHLALAADPAFCASLNA-ELDLEEH
hT1R3,        305 TSDLVMGLPGMAQMGTVLGFLQRGAQLHEFPQYVKTHLALATDPAFCSALGEREQGLEED
                  ****** **  *  *********** * **  ** ****** *****  *   *  ***

mT1R3h.729    364 VMGQRCPQCDDIMLQNLSSGLLQNLSAGQLHHQIFATYAAVYSVAQALHNTLQCNVSHCH
hT1R3,        365 VVGQRCPQCDCITLQNVSAGLN--------HHQTFSVYAAVYSVAQALHNTLQCNASGCP
                  * ******** * *** * **         *** *  ******************** * *

mT1R3h.729    424 VSEHVLPWQLLENMYNMSFHARDLTLQFDAEGNVDMEYDLKMWVWQSPTPVLHTVGTFNG
hT1R3,        417 AQDPVKPWQLLENMYNLTFHVGGLPLRFDSSGNVDMEYDLKLWVWQGSVPRLHDVGRFNG
                      * **********  **   * * **  ********** ****   * ** ** ***

mT1R3h.729    484 TLQLQQSKMYW--PGNQVPVSQCSRQCKDGQVRRVKGFHSCCYDCVDCKAGSYRKHPDDF
hT1R3,        477 SLRTERLKIRWHTSDNQKPVSRCSRQCQEGQVRRVKGFHSCCYDCVDCEAGSYRQNPDDI
                   *     *  *    ** *** *****  ********************* *****  ***

mT1R3h.729    542 TCTPCNQDQWSPEKSTACLPRRPKFLAWGEPVVLSLLLLLCLVLGLALAALGLSVHHWDS
hT1R3,        537 ACTFCGQDEWSPERSTRCFRRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLFVHHRDS
                   ** * ** **** ** *  **  ******* ** ***** * *** ****** *** **

mT1R3h.729    602 PLVQASGGSQFCFGLICLGLFCLSVLLFPGRPSSASCLAQQPMAHLPLTGCLSTLFLQAA
hT1R3,        597 PLVQASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLSTLFLQAA
                  ********   **** **** ********** ** * ******  ****************

mT1R3h.729    662 ETFVESELPLSWANWLCSYLRGLWAWLVVLSATFVEAALCAWYLTAFPPEVVTDWSVLPT
hT1R3,        657 EIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTDWHMLPT
                  * ***********  *   *** ******* *  ** *** *** **********  ***

mT1R3h.729    722 EVLEHCH-----SFGLAHATNATLAFLCFLGTFLVRSQPGCYNRARGLTFAMLAYFITWV
hT1R3,        717 EALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGCYNRARGLTFAMLAYFITWV
                  * * **      ************************************************
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mT1R3h.729    777 SFVPLLANVQVANVQVAYQPAVQMGAILVCALGILVTFHLPKCYVLLWLPKLNTQEFFLG
hT1R3,        777 SFVPLLANVQVV-----LRPAVQMGALLLCVLGILAAFHLPRCYLLMRQPGLNTPEFFLG
                  ***********         ******* * * ****  **** ** *   * *** *****

mT1R3h.729    837 RNAKKAADENSG
hT1R3,        832 GGPGDAQGQNDG
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